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Ethnic Differences in the Prognostic Value of Stress Technetium-99m Tetrofosmin Gated Single-Photon Emission Computed Tomography Myocardial Perfusion Imaging

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OBJECTIVES This study was designed to evaluate the differential prognostic value of gated single-photon emission computed tomographic imaging (SPECT) imaging in an ethnically diverse multicenter registry.

BACKGROUND Ethnic minority patient populations have reportedly higher coronary heart disease mortality with greater comorbidity and a clustering of risk factors at a significantly younger age when compared with Caucasian, non-Hispanic patients. Despite our increasingly diverse population, the predictive accuracy of cardiac imaging in ethnic minority patients is ill-defined.

METHODS A total of 7,849 patients were prospectively enrolled in a registry of patients undergoing exercise (44%) or pharmacologic stress (56%) technetium-99m tetrofosmin SPECT. Scans were scored using a 20-segment myocardial model with a 5-point severity index. Multivariable Cox proportional hazards models were employed to assess time to death or myocardial infarction.

RESULTS A total of 1,993 African-American, 464 Hispanic, and 5,258 Caucasian non-Hispanic patients underwent SPECT imaging. African-American and Hispanic patients more often had a history of stroke, peripheral arterial disease, angina, heart failure, diabetes, hypertension, and smoking at a younger age. Moderate or severely abnormal SPECT scans were noted in 21%, 17%, and 13% of African-American, Hispanic, and Caucasian non-Hispanic patients, respectively ($p < 0.0001$). Cardiovascular death rates were highest for ethnic minority patients ($p < 0.0001$). Annual rates of ischemic heart disease death ranged from 0.2% to 3.0% for Caucasian non-Hispanic and 0.8% to 6.5% for African-American patients with low-risk to severely abnormal SPECT scans ($p < 0.0001$). For post-stress ejection fraction <45%, annualized risk-adjusted death rates were 2.7% for Caucasian non-Hispanic patients versus 8.0% and 14.0% for African-American and Hispanic patients ($p < 0.0001$).

CONCLUSIONS The current results from a large observational registry reveal that exercise and pharmacologic stress SPECT effectively predicts major cardiovascular events in a large cohort of African-American and Hispanic patients evaluated for suspected myocardial ischemia. These results provide further evidence that ethnic minority patient populations have a worsening outcome related to cardiovascular disease. (J Am Coll Cardiol 2005;45:1494–504) © 2005 by the American College of Cardiology Foundation

Stress myocardial perfusion imaging is routinely employed both for coronary disease detection and risk assessment in approximately 7 million patients annually in the U.S. Despite an ever-increasingly ethnically diverse U.S. population, our current understanding of the predictive accuracy of cardiac testing in African-American and other ethnic minority populations is limited (1,2). Current epidemiologic data are greatest for African Americans and notable for having a higher mortality associated with coronary artery disease (3,4). It has been postulated that higher overall coronary heart disease mortality in African Americans is related to more out-of-hospital deaths, greater comorbidity, and a higher prevalence and clustering of traditional cardiac risk factors (5). However, the reported lower prevalence and extent of obstructive coronary artery disease and coronary calcification in African Americans compared with Caucasian non-Hispanic patients evidences our lack of understanding of ethnic differences in disease mechanisms and outcomes (6–8).

Because of a greater risk factor and comorbidity burden, it may be hypothesized that ethnic minority patient populations might have specific challenges that limit the predictive accuracy of noninvasive cardiac tests for the estimation

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Abbreviations and Acronyms

EF = ejection fraction
MI = myocardial infarction
SPECT = single-photon emission computed tomographic imaging
Tc = technetium
Tl = thallium

of near-term outcome. The purpose of the current report was to evaluate the differential prognostic value of the extent and severity of myocardial perfusion and left ventricular function measurements from gated single-photon emission computed tomographic imaging (SPECT) imaging in a ethnically diverse multicenter registry.

METHODS

Patient inclusion. Five geographically diverse centers enrolled 7,849 consecutively tested outpatients in a prospectively designed multicenter registry of technetium (Tc)-99m tetrofosmin SPECT; 134 Asian patients were excluded because of low statistical power for outcome analysis and our inability to discern ethnicity type (e.g., Indian). Site enrollment was 20% from Duke University Medical Center, 18% from Georgetown University Medical Center, 18% from Emory University Veterans Administration Hospital, 14% from Rush University Medical Center, and 30% from University of California at Los Angeles Medical Center. Patients gave informed consent and underwent SPECT for clinically referred reasons from April 1, 1997, to December 31, 1999. Patient enrollment occurred during the initial (approximate) 1 year of this study, with average daily site enrollment of ~8 to 12 patients. A previous report included patients with low-risk perfusion SPECT was published (9).

Data collection procedures. Data elements, definitions, and procedures were prospectively defined and uniformly applied across all institutions.

Stress testing procedures. A total of 3,442 patients underwent symptom-limited exercise testing using a modified or standard Bruce protocol. Heart rate, blood pressure, and 12-lead electrocardiograms were recorded before (supine and upright positions) and during each minute of exercise and recovery. Standards for test conductance and termination were consistent with the current guidelines (10). Patients exercised until the point of volitional fatigue unless marked electrocardiographic abnormalities, hemodynamic instability, chronotropic incompetence, ventricular tachycardia or fibrillation, or disabling chest pain symptoms occurred. Exercise was discontinued if exertional hypotension, malignant ventricular arrhythmias, marked ST-segment depression, or limiting chest pain occurred. An abnormal electrocardiogram was defined as ≥1 mm ST-segment depression (J point + 60 ms) developed from rest to peak stress.

Pharmacologic stress testing. Adenosine or dipyridamole pharmacologic stress testing was performed in 37% and 11% of patients, respectively. The remaining 8% of patients underwent dobutamine SPECT. Dipyridamole was infused at 0.142 mg/kg/min for 4 min (11). Patients exhibiting persistent side effects were administered 75 to 125 mg of aminophylline intravenously followed by nitroglycerin as needed. Adenosine was infused intravenously at a dose of 140 mg/kg/min over 6 min, with administration of the radiopharmaceutical at the midpoint of the infusion (11).

Dobutamine was infused using standard incremental dosing from 5 to 40 μg/kg/min, during which patients remained under continuous clinical and electrocardiographic monitoring (11). Test end points included completion of the final stage of the protocol, severe ischemia (severe angina, >2 mm ST-segment depression), hypertension (systolic blood pressure >220 mm Hg), hypotension (drop in systolic blood pressure >20 mm Hg), arrhythmias, or side effects intolerable to the patient. Atropine (1 mg intravenous) was used in patients who failed to attain 85% of age-predicted maximal heart rate at peak dose.

During testing, each patient was queried for symptoms of chest pain, dyspnea, fatigue, flushing, headache, nausea, and dizziness.

SPECT procedures. The SPECT protocol utilized at each site was previously described (9) and performed in accordance with usual practice at each institution. For SPECT imaging, rest and stress Tc-99m (10% of patients) or thallium (Tl)-201 rest/Tc-99m stress (90% of patients) tetrofosmin was performed. Tomographic imaging was performed immediately following exercise and during the resting state using a gamma camera with a computer interface where acquisitions were performed over a 180° semicircular orbit. Data were acquired in a 64 × 64 matrix for 32 and 64 projections for Tl-201 and Tc-99m in a step-and-shoot format. Each image set (horizontal and vertical long-axis and short-axis planes) was normalized to maximal myocardial activity.

20-Segment myocardial model interpretation. Each scan was interpreted using a 20-segment myocardial model (12). Segments were graded using a 5-point scoring system ranging from 0 (normal) to 4 (absent perfusion). The 20-segment myocardial model has been previously reported and validated (11–13). Scores were summed from rest and stress scans to derive the summed rest and stress score. The difference between the summed stress and rest score is the amount of inducible ischemia or summed difference score. Risk-based categories for the summed stress score are low risk (scores 0 to 3), mildly abnormal (scores 4 to 8), moderately abnormal (scores 9 to 13), and severely abnormal (scores >13). We also categorized post-stress gated ejection fraction (EF) values <45% and ≥45% (n = 4,575).

Scans were interpreted by an experienced investigator blinded to the patient's clinical history, ethnicity, and stress test results.

Follow-up procedures. Each patient gave informed consent for the follow-up portion of this study. Each center had institutional review board approval for this registry and for the collection of follow-up data. Patients were contacted at

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Table 1. Past Medical History by Ethnic Subsets of the Stress Testing Registry

	African American (n = 1,993)	Hispanic (n = 464)	Caucasian Non-Hispanic (n = 5,258)	p Value
Age (yrs)	62 ± 12	60 ± 12	63 ± 11	< 0.0001
Female gender	41%	52%	34%	< 0.0001
History of coronary disease	16%	21%	39%	< 0.0001
Prior myocardial infarction	9%	8%	16%	< 0.0001
History of stroke	5%	4%	0.6%	< 0.0001
History of congestive heart failure	15%	18%	3%	< 0.0001
History of COPD	0.4%	0%	0.2%	< 0.0001
History of renal failure	3%	3%	0.4%	< 0.0001
History of liver disease	0%	0%	0.1%	0.261
Prior cancer	0.5%	1%	0.7%	< 0.0001
History of PAD	10%	10%	1%	< 0.0001
Prior coronary bypass surgery	8%	10%	16%	< 0.0001
Prior PCI	5%	4%	10%	< 0.0001
Prior stent	2%	0%	6%	< 0.0001
Prior catheterization	7%	5%	18%	< 0.0001
Prior valve surgery	0.2%	0%	2%	< 0.0001
Prior heart transplant	0%	0.6%	0.1%	0.016
Other transplant	1%	1%	0.5%	0.013
Cardiac risk factors				
Current smoker	50%	35%	18%	< 0.0001
Prior smoker	5%	0%	30%	< 0.0001
Family history of CAD	39%	34%	29%	< 0.0001
Hypertension	64%	73%	48%	< 0.0001
Hypercholesterolemia	4%	4%	29%	< 0.0001
Non–insulin-dependent DM	22%	28%	10%	< 0.0001
Insulin-dependent DM	8%	13%	8%	< 0.0001

CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; PAD = peripheral arterial disease; PCI = percutaneous coronary intervention.

six months and then yearly thereafter. During the telephone contact, an experienced nurse or physician completed a scripted interview in which each patient or a family member was queried for the occurrence of death and major cardiovascular events or hospitalizations.

Major adverse events included all-cause or cardiovascular death and hospitalization for acute myocardial infarction (MI), as well as the use of coronary revascularization procedures. Cardiovascular death was defined as that related to stroke, congestive heart failure, fatal MI, sudden cardiac death, or complications associated with cerebrovascular or peripheral arterial disease. An ischemic death was defined as that related to ischemic cardiomyopathy, sudden cardiac death, or fatal MI.

When a cardiac event was identified, medical records were reviewed or the referring physician was contacted to confirm the date and event circumstances. For all deaths, a death certificate was requested. This confirmation was conducted under the guidance of each site's human investigations committee and performed by an experienced physician blinded to the clinical and stress test data. Follow-up was complete in 99% of patients. Time to follow-up for surviving patients was a median of 1.6 years (25th to 75th percentile 1.2 to 2.0).

Statistical analyses. Continuous variables were summarized as means ± SD and categorical variables as percentages. Continuous variables were compared within subsets by analysis of variance techniques. Categorical variables were compared using a chi-square statistic. A probability value of <0.05 was considered statistically significant.

This study's primary end point was time to cardiovascular death and the secondary end point was death or nonfatal MI. Cardiovascular death was subdivided as total cardiovascular and ischemic heart disease-related death.

We examined the univariable relations of clinical and stress variables to freedom from death and death or nonfatal MI. The Cox proportional hazards model was used to examine individual relations between clinical and stress imaging variables and outcome. Individual models estimating the relationship between SPECT and outcome were risk-adjusted by controlling for covariates (age, gender, diabetes, hypertension, smoking, angina, stroke or coronary disease history, heart failure, and peripheral arterial disease; the summed difference score was added to predictive models including EF). From the multivariable models, risk-adjusted relative risk ratios and 95% confidence intervals were calculated. A stratified Cox model was employed to calculate differences in survival for patients undergoing exercise and pharmacologic stress. A test for interaction of ethnicity by gender was calculated. A Bonferroni correction was applied for multiple comparisons.

RESULTS

Past medical history and presenting symptoms by SPECT results (Table 1). African-American and His-

Table 2. Stress Test Results by Ethnic Subsets of the Stress Testing Registry

	African American (n = 1,993)	Hispanic (n = 464)	Caucasian Non-Hispanic (n = 5,258)	p Value
Medications at testing				
Digoxin	7%	3%	6%	0.03
Aspirin	8%	0.6%	14%	< 0.0001
Nitroglycerin	16%	19%	8%	< 0.0001
Calcium channel blocker	36%	22%	18%	< 0.0001
Beta-blocker	33%	26%	22%	< 0.0001
ACE inhibitor	8%	0%	15%	< 0.0001
Statin	15%	11%	36%	< 0.0001
Other lipid	0.4%	0%	1%	0.006
Hormone replacement	1%	1%	4%	< 0.0001
Patient presenting symptoms				< 0.0001
None	13%	9%	32%	
Nonanginal	32%	29%	13%	
Atypical	1%	1%	10%	
Typical	51%	61%	42%	
Dyspnea	2%	0.2%	3%	
Rest agent				< 0.00001
TI-201	85%	95%	92%	
Tetrofosmin	15%	5%	8%	
Abnormal rest ECG	43%	44%	37%	< 0.0001
ECG evidence of MI	7%	6%	7%	0.96
ECG response to stress				< 0.00001
Nonischemic	81%	83%	62%	
Ischemic	10%	10%	18%	
Equivocal	8%	7%	14%	
Dyspnea	1%	0%	6%	
Exercise stress	49%	43%	42%	< 0.0001
Exertional chest pain				< 0.0001
None	98%	95%	94%	
Nonlimiting	1%	2%	5%	
Limiting	1%	3%	1%	
Rest heart rate	73 ± 19	66 ± 16	71 ± 32	0.47
Peak exercise heart rate	119 ± 38	114 ± 33	125 ± 36	< 0.0001
Rest blood pressure	164/82	141/80	143/78	DBP p < 0.0001 SBP p = 0.10
Peak exercise blood pressure	163/79	158/77	169/78	DBP p = 0.061 SBP p < 0.0001
Total exercise time	6.7 ± 4	6.4 ± 4	7.8 ± 4	< 0.00001
Post stress EF (n = 4,575)	68 ± 7	59 ± 6	58 ± 7	0.10

Peak exercise heart rate and blood pressure values excluded for those undergoing pharmacologic stress imaging.
ACE = angiotensin-converting enzyme; DBP = diastolic blood pressure; ECG = electrocardiogram; EF = ejection fraction; MI = myocardial infarction; SBP = systolic blood pressure.

panic patients were more often women ($p < 0.0001$) and less likely to have a prior history of coronary disease or revascularization procedure ($p < 0.0001$) as compared with Caucasian non-Hispanic patients ($p < 0.0001$). In general, African-American and Hispanic patients had a greater degree of comorbidity including more prior stroke, heart failure symptoms, peripheral arterial disease, as well as a greater frequency and clustering of traditional cardiac risk factors (all $p < 0.0001$).

Stress test characteristics (Table 2). African-American and Hispanic patients were more likely to have ST-T wave changes or Q waves on their resting electrocardiogram ($p < 0.0001$ for both). They also had a lower frequency of ischemic ST-segment changes noted during stress testing, with more than 80% of African-American and Hispanic patients having a negative stress electrocardiogram ($p < 0.0001$). Greater physical work capacity (higher peak exercise heart rates and exercise times) was noted for Caucasian non-Hispanic patients ($p < 0.0001$).

Figure 1 notes the frequency of the summed stress score risk groups by racial and ethnic cohorts. Nearly two-thirds of African-American and Hispanic patients had a low risk-summed stress score as compared with 77% of Caucasian non-Hispanic patients ($p < 0.0001$). The incidence of moderate or severely abnormal SPECT scans was greatest for ethnic minority subsets (approximately 20% of African-American and Hispanic patients vs. 13% of Caucasian non-Hispanic patients, $p < 0.0001$). Similarly, African-American patients had the highest rate of an abnormal post-stress left ventricular EF <45% (10% vs. 7% for Caucasian non-Hispanic and 8% for Hispanic patients, $p = 0.02$).

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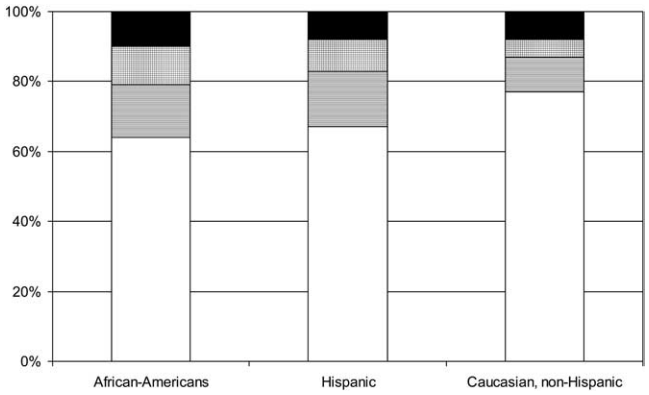

Figure 1. Frequency of low risk, mildly abnormal, moderately abnormal, and severely abnormal summed stress scores in African American, Hispanic, and Caucasian non-Hispanic patients. **Black bars** = severe; **hatched bars** = moderate; **dotted bars** = mild; **white bars** = low. $p < 0.0001$.

Rates of death from all causes, cardiovascular disease, and ischemic heart disease (Tables 3 and 4). During 2 years of follow-up, there were a total of 675 deaths from all causes. Of the total deaths, 133 were from cardiovascular disease and 96 from ischemic heart disease. Additionally, 460 patients were admitted to the hospital for acute MI. Nearly 1 in 10 (n = 666) patients underwent a coronary revascularization procedure during 2-years of follow-up; 279 were coronary stent procedures and 218 were coronary artery bypass surgery. Ninety-day and two-year rates of other important cardiovascular events and coronary revascularization use by SPECT imaging results are reported by ethnicity in Table 4.

Figure 2 depicts the annualized rates of death for each racial and ethnic subset of the current series by their summed stress score risk group. In general, higher rates of death from all causes and cardiovascular disease were noted for African-American and Hispanic patients as compared with their Caucasian non-Hispanic counterparts ($p < 0.0001$). For African-American patients, the all-cause death rates ranged from 3.5% to 9% per year for low risk to severely abnormal SPECT scans ($p < 0.0001$). For Hispanic patients, the annual rates of cardiovascular death ranged from 2.4% to 11.5% for low-risk to high-risk SPECT scans ($p < 0.0001$). By comparison, the annualized ischemic heart disease death rates were 0.2% to 2.8% for Caucasian non-Hispanic patients with a low- to high-risk SPECT scan ($p < 0.0001$).

Measures of post-stress left ventricular function were also highly predictive of outcome in all ethnic patient subsets, even after controlling for age, history of coronary disease, heart failure symptoms, and the summed difference score ($p < 0.0001$). However, differences in survival were noted by ethnicity. Using a cutpoint of post-stress EF <45% (n = 338), annualized risk-adjusted death rates were 2.7% for Caucasian non-Hispanic as compared with 8.0% and 14.0% for African-American and Hispanic patients, respectively ($p < 0.0001$). In a subset analysis of patients with a low risk-summed stress score, post-stress EF was highly predictive of cardiac death ($p < 0.0001$), with the African-American and Hispanic patients having a 2% ($p < 0.0001$) and 3% ($p < 0.0001$) increased risk of death in the setting of low-risk perfusion when compared with Caucasian non-Hispanic patients.

The time to cardiovascular death or nonfatal MI is plotted in Figures 3A and 3B for African-American, Hispanic, and Caucasian non-Hispanic patients (model chi-square = 192, $p < 0.00001$). At two years, the overall rate of event-free survival was 96% for Caucasian non-Hispanic patients with a low risk SPECT as compared with 93% and 91% for African-American and Hispanic patients, respectively ($p < 0.0001$). Decrementally worsening event-free survival was noted with an increasing extent and severity of the summed stress score but was lowest, at approximately 60% to 65%, for African-Americans and Hispanics with severely abnormal SPECT scans ($p < 0.0001$). Of the low risk, those with a summed stress score of 0 had higher event-free survival ($p < 0.0001$) where 2-year event-free survival was 94% for African-American, 91% for Hispanic, and 97% for Caucasian non-Hispanic patients, respectively ($p < 0.0001$).

For Caucasian non-Hispanic patients, 2-year event-free survival was 97% versus 86% for EF measures ≥45% and <45% ($p < 0.0001$). For African-American patients, 2-year

Table 3. Overall Rates of Major Adverse Cardiovascular Events

	African American (n = 1,993)	Hispanic (n = 464)	Caucasian Non-Hispanic (n = 5,258)	p Value
Deaths				0.001
Fatal myocardial infarction	0.4%	0.0%	0.3%	
Stroke	0.2%	0.6%	0.2%	
Sudden cardiac death	0.2%	0.0%	0.2%	
Other vascular	4.0%	4.5%	2.8%	
All causes	7.8%	16.2%	8.3%	
Nonfatal myocardial infarction	1.7%	2.6%	9.2%	< 0.0001
Unstable angina	1.3%	2.2%	6.9%	< 0.0001
Stroke	0.7%	0.6%	1.0%	0.198
Congestive heart failure first admission	1.4%	0.9%	2.1%	< 0.0001
Other chest pain	5.3%	3.9%	13.9%	< 0.0001

Table 4. Comparative Analysis of Ethnicity by SPECT Imaging Results for 90-Day and 2-Year Hospitalization Rates for Nonfatal Cardiovascular Events and Revascularization Procedures

	African American (n = 1,993)	Hispanic (n = 464)	Caucasian Non-Hispanic (n = 5,258)	p Value
Unstable angina				< 0.0001
At 90 days				
Mildly abnormal	0.2%	0.0%	0.8%	
Moderate-severely abnormal	0.3%	0.2%	1.7%	
At 2 years				
Mildly abnormal	4.5%	8.8%	7.5%	
Moderate-severely abnormal	7.5%	18.0%	15.0%	
Acute myocardial infarction				< 0.0001
At 90 days				
Mildly abnormal	0.6%	1.1%	1.2%	
Moderate-severely abnormal	0.9%	1.7%	1.7%	
At 2 years				
Mildly abnormal	4.7%	4.5%	13%	
Moderate-severely abnormal	7.0%	6.5%	17%	
Chest pain hospitalization				< 0.0001
At 90 days				
Mildly abnormal	0.4%	0.3%	2.4%	
Moderate-severely abnormal	1.0%	0.6%	4.3%	
At 2 years				
Mildly abnormal	17.5%	13.0%	19.0%	
Moderate-severely abnormal	26.0%	22.0%	31.0%	
Stroke				0.25
At 90 days				
Mildly abnormal	0.1%	0.0%	0.2%	
Moderate-severely abnormal	0.1%	0.0%	0.4%	
At 2 years				
Mildly abnormal	1.8%	3.0%	1.4%	
Moderate-severely abnormal	2.5%	2.3%	2.5%	
Congestive heart failure				< 0.0001
At 90 days				
Mildly abnormal	0.3%	0.0%	0.3%	
Moderate-severely abnormal	0.4%	0.0%	0.5%	
At 2 years				
Mildly abnormal	3.4%	3.0%	5.7%	
Moderate-severely abnormal	5.3%	4.8%	7.3%	

event-free survival was 94% versus 76% for those with measurements ≥45% and <45% ($p < 0.0001$). Similarly, for Hispanic patients survival was 92% and 70% for those whose post-stress EF was ≥45% and <45% ($p < 0.0001$). Figure 4 depicts a scatterplot of post-stress EF measures by annualized rates of cardiovascular death or MI for each ethnic subset.

Risk-adjusted Cox proportional hazards model (Figs. 5 and 6). In a risk-adjusted Cox regression analysis (controlling for age, gender, diabetes, hypertension, smoking status, angina, history of stroke or coronary disease, heart failure symptoms, and peripheral arterial disease), the relative risk ratios for cardiac death or nonfatal MI were 1.6- and 1.4-fold higher for African-American and Hispanic patients with mildly abnormal SPECT scans as compared to Caucasian non-Hispanic patients (Fig. 5, $p < 0.0001$). For moderately abnormal SPECT scans, the relative risk ratios were 2.3- to 5.6-fold higher for non-Caucasian non-Hispanic patients ($p < 0.0001$). Similarly, for severely abnormal scans, the relative risk ratios were 3.7- and 4.1-fold higher for African-American and Hispanic patients as compared with Caucasian non-Hispanics ($p < 0.0001$). Of note, the relative risk ratio confidence intervals included 1.0 for Hispanic patients with mildly abnormal scans.

Using a stratified Cox model, the differential in relative risk was greatest for patients undergoing vasodilator stress imaging (Fig. 6). Relative risk ratios were 2.1- to 6.5-fold and 1.8- to 4.8-fold higher for African-American and Hispanic patients, respectively, as compared with Caucasian non-Hispanics ($p < 0.0001$).

Tests for interaction (gender by ethnicity). We further explored the relationship of gender and ethnicity upon the estimation of cardiac death or MI using a two-way interaction ($p = 0.006$). For women, the risk of death or MI was elevated 2.7- to 9.0-fold in African-American ($p = 0.006$) and Hispanic ($p < 0.0001$) females with a moderate-severely abnormal SPECT scan. Additionally, Hispanic (relative risk = 5.6, 95% CI = 2.3 to 13.8, $p < 0.0001$) women with mildly abnormal scans also had a higher risk of death or infarction when compared to their Caucasian non-Hispanic

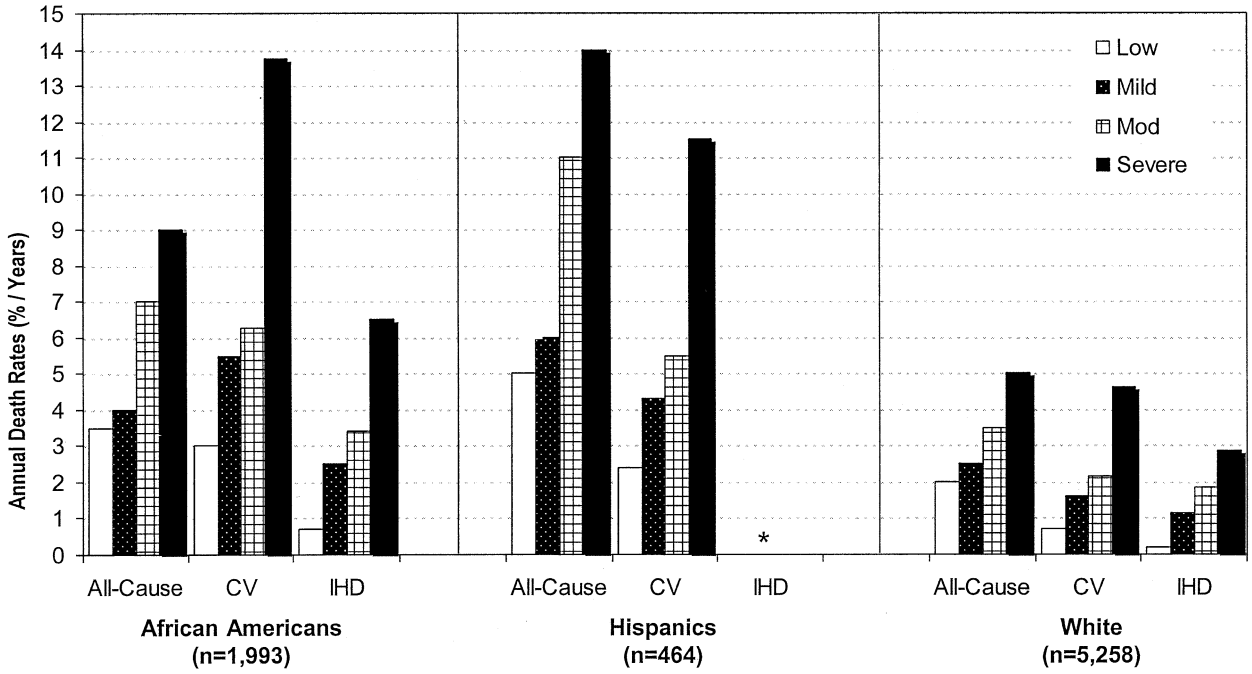

Figure 2. Estimated annual death rates by summed stress score risk group in African-American, Hispanic, and Caucasian non-Hispanic patients. All-cause death: chi-square = 33, $p < 0.0001$; cardiovascular death: chi-square = 127, $p < 0.0001$; ischemic heart disease death: chi-square = 109, $p < 0.0001$. CV= cardiovascular; IHD = ischemic heart disease. *No ischemic heart disease deaths reported.

counterparts. The proportional risk was elevated 7.4% to 12% for African American and Hispanic women with an abnormal SPECT scan as compared with Caucasian non-Hispanic women, respectively.

DISCUSSION

The current results support prior evidence that ethnic minority patient populations have a disproportionate burden of worsening outcome related to cardiovascular disease (14). Prior evidence, in largely Caucasian non-Hispanic populations, suggests that noninvasive stress testing may be used to assess a patient's risk of major adverse cardiac events (10). In contrast to prior reports, we compared the prognostic value of SPECT imaging results in a large cohort of African-American and Hispanic stable outpatients. Our results reveal that risk stratification is highly effective at predicting cardiac death and MI in a large cohort of African-American and Hispanic patients based upon exercise and pharmacologic stress myocardial perfusion and ventricular function measures. Notably, African-American and Hispanic patients had a greater risk of events at all levels of SPECT scan severity as compared with Caucasian non-Hispanic patients (10). Adjustments for baseline group differences did not significantly alter these results.

Differential prognosis and coronary disease extent in racial and ethnic subsets. Higher coronary heart disease death rates have been reported in ethnic minority populations; in particular a higher risk profile at younger ages when compared with Caucasian non-Hispanic cohorts (2–5,14). Numerous investigators have proposed that increases in risk factor prevalence and clustering across racial and ethnic minority populations are an explanation for the excess cardiovascular mortality (3–5,14). Notably, these prior reports also demonstrate less obstructive coronary disease on angiography and less extensive coronary calcification, suggesting an uncoupling between risk factor burden and coronary stenosis extent and severity (3–5,8). The current results demonstrate that there is a higher prevalence of stress-induced perfusion abnormalities in minority populations. Ethnic minority patients with stress-induced myocardial perfusion and ventricular function abnormalities were associated with a higher risk of cardiovascular death at all levels of scan severity and similarly point to ethnic differences in coronary disease pathophysiology. That is, there is a notable increased risk of events in the setting of abnormal perfusion abnormalities.

However, overall rates of acute coronary syndromes were significantly higher for Caucasian non-Hispanics (Table 3). Thus, ethnic differences in event rates appear to be largely driven by fatal ischemic and other vascular events. Issues of financial means, health care access, and having a regular source of care may affect differential hospitalization rates for ethnic minority patients (3–5,14). From the current series, the decidedly higher rates of diabetes in our ethnic minority patients could result in a greater frequency of silent MIs due to the prevalence of diabetic neuropathy. This is supported by an increased incidence of significant Q waves on minority patient's resting electrocardiogram (Table 2).

Racial and ethnic differences in cardiac imaging. Limited prior research suggests that phenotypic differences in coronary disease imaging between ethnic groups may explain

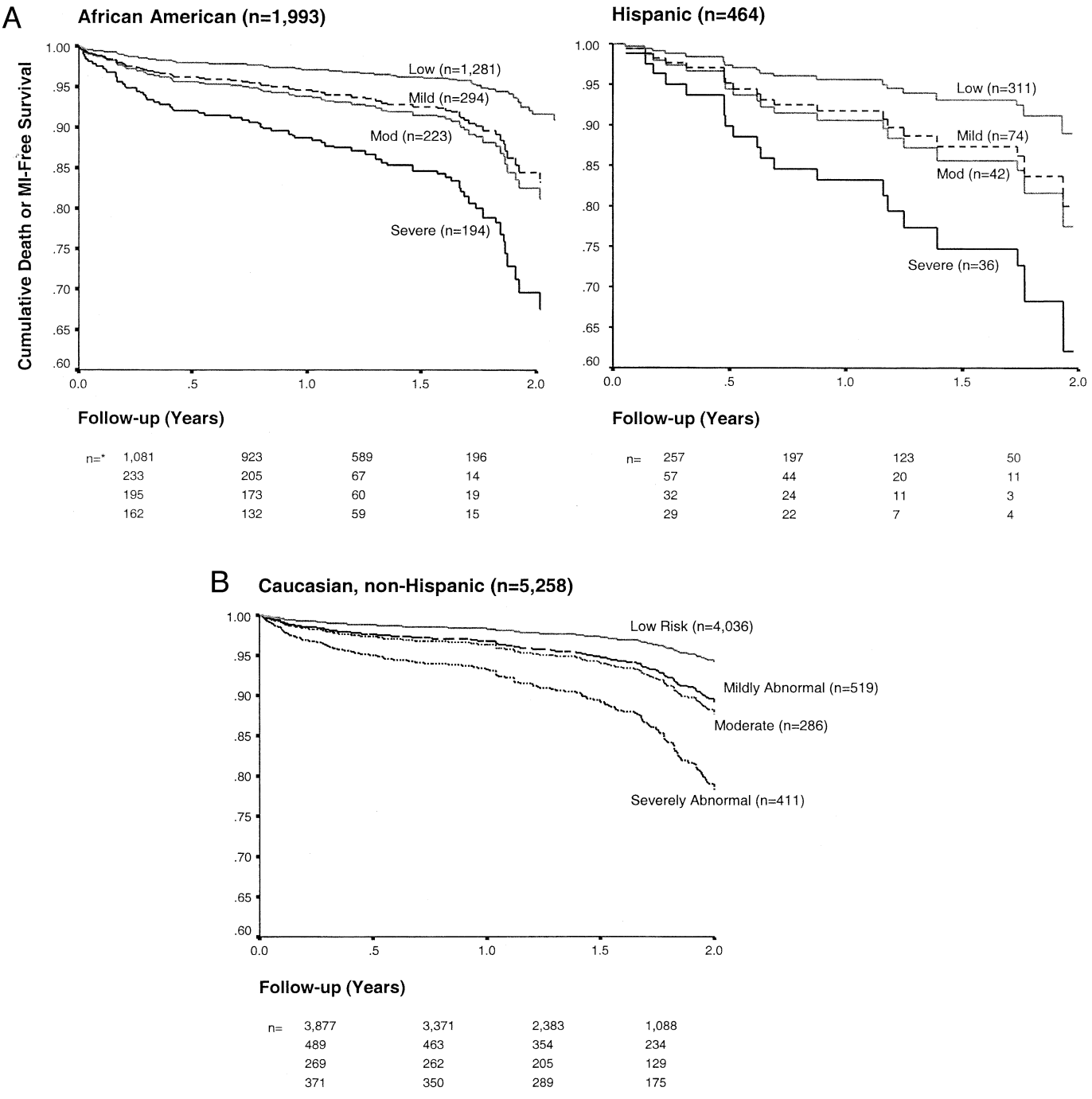

Figure 3. **(A)** Survival free from cardiovascular death or myocardial infarction in African-American and Hispanic patients. Model chi-square = 192; $p < 0.0001$. *n = available sample every 0.5 years of follow-up for low, mild, moderate, and severely abnormal scans. **(B)** Survival free from cardiovascular death or myocardial infarction in Caucasian non-Hispanic patients. Model chi-square = 192; $p < 0.0001$. *n = available sample every 0.5 years of follow-up for low, mild, moderate, and severely abnormal scans. Asian patients were not included in this analysis because of small sample scans.

differences in outcome (7,8,15–19). For ethnic minority patients, differences with regards to vascular function or vasomotor responsiveness, which are modulated by a patient's risk factor burden, may facilitate higher event risk at any level of obstructive coronary disease burden. In the current series, we noted a higher prevalence and worsening risk with inducible myocardial perfusion abnormalities for African-American and Hispanic patients. For the largest ethnic minority population discussed herein, African Americans, higher rates and protracted years of hypertension (14,20) promote focal and generalized retinal artery narrowing leading to greater rates of carotid plaque, stroke, and MI (21). Asymptomatic African Americans enrolled in the CARDIA study also exhibited a higher diastolic and systolic reactivity to stress, leading to a greater proclivity toward hypertension development (22). Additionally, published re-

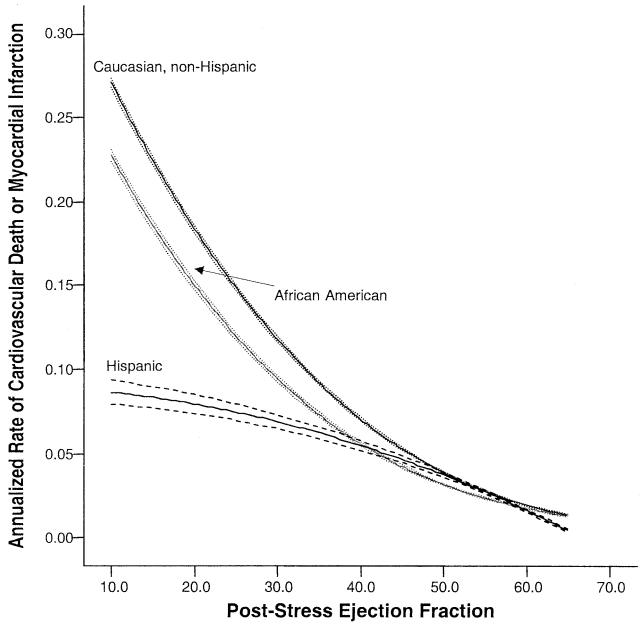

Figure 4. Annualized risk-adjusted cardiovascular death or myocardial infarction rate by post-stress left ventricular ejection fraction for African-American, Hispanic, and Caucasian non-Hispanic patients. Line of best fit was a cubic spline fit with 95% confidence intervals.

ports on brachial artery reactivity testing in African Americans have noted a greater prevalence of endothelial dysfunction (23).

Our results also reveal a greater prevalence and risk associated with moderate or severely abnormal myocardial perfusion imaging in ethnic minority patients as compared with Caucasian non-Hispanic patients. Synthesizing this evidence suggests that physiologic abnormalities may play a greater role in risk assessment than does obstructive disease burden for ethnic minority patients. Prior evidence on racial differences in cardiac stress testing is limited to very small series of patients (1,2). The majority of prognostic data are largely based on Caucasian non-Hispanic populations. A synthesis of this evidence reports that normal perfusion is associated with an exceedingly low rate of cardiac death or MI (i.e., <1% per year) (13). In the current ethnically diverse series, risk stratification resulted in patients with a low-risk scan having an associated death rate exceeding 1% over 2 years for African-American and Hispanic patients (24,25). Similarly, Akinboboye et al. (2) noted a similarly high 2% annual risk of major cardiovascular events in 592 African-American patients with low risk SPECT results.

Study limitations. Although we enrolled a large cohort of ethnic minority patients, differences among specific subsets may be underpowered, in particular for the small series of Hispanic patients. Despite this, we do have sufficient statistical power to detect differences between African-American and Caucasian non-Hispanic patients. Finally, patient outcomes are influenced multifactorially, and our current predictive models likely fail to account for the gamut of explanatory variance in predictive models. We attempted hierarchical predictive models for all-cause, cardiovascular, and ischemic deaths. Although event classification improved when estimating cardiac events, misclassification of death cause could confound these results. We examined the comparative prognostic value of SPECT imaging across multiple groups; although many of these analyses were highly significant, we did not routinely employ statistical corrections for multiple comparisons.

Conclusions. There is currently a paucity of evidence as to the prognostic value of many commonly performed cardiac diagnostic tests in ethnic minority patients. The recent Na-

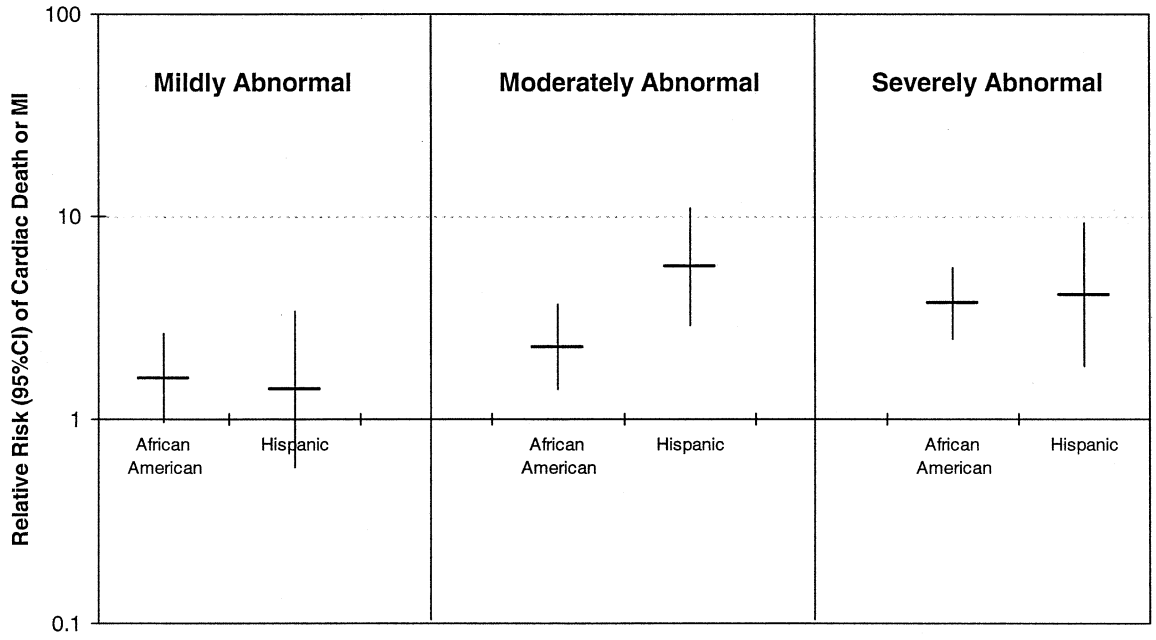

Figure 5. Risk-adjusted relative risk of cardiac death or myocardial infarction (MI) by summed stress score risk in African-American and Hispanic patients versus Caucasian non-Hispanic patients undergoing Tc-99m myoview single-photon emission computed tomographic imaging. CI = confidence interval.

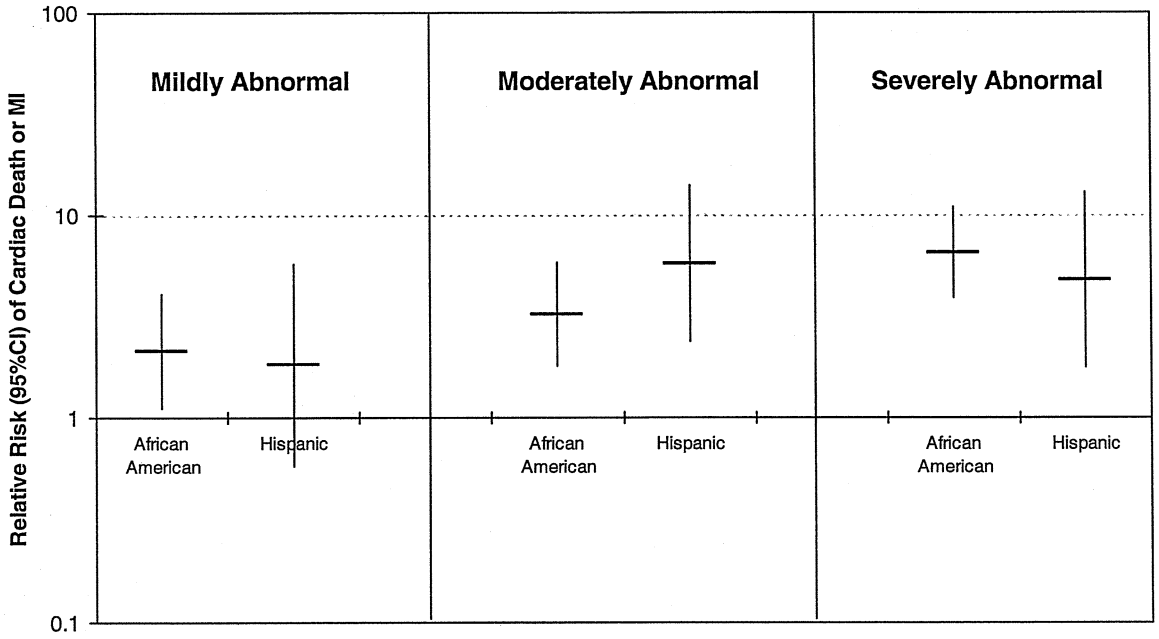

Figure 6. Risk-adjusted relative risk of cardiac death or myocardial infarction (MI) by summed stress score risk in African-American and Hispanic patients versus Caucasian non-Hispanic patients undergoing adenosine/dipyridamole Tc-99m myoview single-photon emission computed tomographic imaging. CI = confidence interval.

tional Healthcare disparities report, released by the Department of Health and Human Services, recognized that racial and ethnic disparities in health care were a national problem (26). Unraveling differences in health care disparities are complex and may be affected by clinical, genetic, and financial differences that influence clinical outcomes. Furthermore, in many urban environments, there is a growing diversity of stress testing laboratory populations, including a greater representation of African-American and Hispanic patients. Rapid population shifts in ethnicity may challenge the health care system and further contribute to suboptimal health care for minorities. In fact, our results from a prospectively designed multicenter registry of 7,849 patients include greater ethnic and racial diversity than previously reported.

A synopsis of this evidence reveals that SPECT imaging is capable of providing prognostication based upon the extent and severity of perfusion abnormalities as well as with gated EF results for African-American and Hispanic patients. As ethnic minority patients have a greater degree of comorbidity and vascular disease, higher than expected cardiovascular events were noted within low- to high-risk SPECT results when compared with Caucasian non-Hispanic patients. Thus, for African-American and Hispanic patients, post-SPECT management strategies should aggressively focus on ameliorating their ischemic and atherosclerotic disease burden. For our ethnic minority patients, a differential threshold for initiation of targeted care should be considered even for those patients with mildly abnormal SPECT scans. A greater intensity of post-SPECT treatment may reduce the excess morbidity and mortality for our ethnic minority patients. Unfolding this evidence should aid in developing management strategies optimized for ethnically diverse patient populations.

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